UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,910	04/07/2000	Yadong Huang	06510/121US1	2429

7590 08/12/2003

Bret Field
Bozicevic Field & Francis LLP
200 Middlefield Road
Suite 200
Menlo Park, CA 94025

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	29

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MAILED
AUG 12 2003
GROUP ~~2900~~ 1600

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 24

Application Number: 09/544,910
Filing Date: April 07, 2000
Appellant(s): HUANG ET AL.

Paula A. Borden
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 25, 2003 (Paper No. 23).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issu s

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

(A) The rejection of claims 1, 4-8, and 11 under 35 USC § 112, first paragraph, as containing subject matter that would not sufficiently enabled by Appellants' disclosure for the reasons set forth in section 8 of the final Office action mailed January 13, 2003 (Paper No. 21), has been withdrawn, because the prior art teaches embodiments of the claimed invention and therefore at least to the extent that the claimed invention is anticipated by the prior art of record, the claimed invention is presumed to be enabled by the disclosures of the prior art.

(B) The rejection of claims 5 and 11 under 35 USC § 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter that Appellant's regard as the invention for the reason set forth in section 10 of the final Office action mailed January 13, 2003 (Paper No. 21), has been withdrawn, because the claims may well be broadly interpreted to encompass a method for treating any disease condition associated with elevated plasma levels of VLDL, despite the nature of the association.

Accordingly, the remaining issues on appeal are:

(1) Whether or not Appellants' disclosure of the claimed invention is adequate under 35 USC § 112, first paragraph and thereby necessarily sufficient to reasonably convey to the skilled artisan that Appellants' had possession of the claimed invention at the time the application was filed.

(2) Whether or not embodiments of the claimed generic invention are anticipated under 35 USC § 102(b) by the disclosures of the prior art of record.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 4-8, and 11 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art under 35 USC § 102(b) and Art of R cord Cited as an Evid ntiary Basis for the Rejection of Claims under 35 USC § 112, First Paragraph

Clavey, V., *et al.* "Cell Culture Conditions Determine Apolipoprotein CIII Secretion and Regulation by Fibrates in Human Hepatoma HepG2 Cells". *Cell Physiol. Biochem.* Vol. 9 (1999), pp. 139-149.

Connor, W.E., *et al.* "N-3 Fatty Acids from Fish Oil: Effects on Plasma Lipoproteins and Hypertriglyceridemic Patients". *Annals N.Y. Acad. Sci.* Vol. 683 (Jun. 14, 1993), pp. 16-34.

Ditschuneit, H.H., *et al.* "Postprandial Lipoprotein Metabolism in Obese Patients with Moderate Hypertriglyceridaemia: Effects of Gemfibrozil". *J. Int. Med. Res.* Vol. 20, No. 3 (Jun. 1992), pp. 197-210.

Durrington, P.N., *et al.* "Effects of Two Different Fibric Acid Derivatives on Lipoproteins, Cholesteryl Ester Transfer, Fibrinogen, Plasminogen Activator Inhibitor and Paraoxonase Activity in Type IIb Hyperlipoproteinaemia". *Atherosclerosis.* Vol. 138 (1998), pp. 217-225.

Kasiske, B.L., *et al.* "The Effects of Lovastatin in Hyperlipidemic Patients with the Nephrotic Syndrome". Am. J. Kidney Dis. Vol XV, No. 1 (Jan. 1990), pp. 8-15.

Lesoon-Wood, L.A., *et al.* "Enhancement of Methylcholanthrene-Induced Neoplastic Transformation in Murine C3H 10T1/2 Fibroblasts by Antisense Phosphorothioate Oligodeoxynucleotide Sequences". Cancer Lett. Vol. 147 (1999), pp. 163-173.

Pedreno, J., *et al.* "Platelet Function in Patients with Familial Hypertriglyceridemia: Evidence that Platelet Reactivity Is Modulated by Apolipoprotein E Content of Very Low Density Lipoprotein Particles". *Metabolism.* Vol. 49, No. 7 (Jul. 2000), pp. 942-949.

Pierce, M.L., *et al.* "Construction of a Directed Hammerhead Ribozyme Library: Towards the Identification of Optimal Target Sites for Antisense-Mediated Gene Inhibition". *Nucl. Acids Res.* Vol. 26, No. 22 (1998), pp. 5093-5101.

Sohail, M., *et al.* "Hybridization of Antisense Reagents to RNA". *Curr. Opin. Mol. Therap.* Vol. 2, No. 3 (2000), pp. 264-271.

Wyne, K.L., *et al.* "Rat Granulosa Cell Apolipoprotein E Secretion". *J. Biol. Chem.* Vol. 264, No. 28 (Oct. 5, 1989), pp. 16530-16536.

Yoshino, G., *et al.* "Long-Term Treatment of Hypercholesterolemic Non-Insulin Dependent Diabetes (NIDDM) with Prevastatin (CS-514)". Atherosclerosis. Vol. 75 (1989), pp. 67-72.

(10) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

(A) Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This ground of rejection of the claims under 35 USC § 112, first paragraph is set forth in section 7 of the prior final Office Action, which was mailed January 13, 2003 (Paper No. 21), and has been briefly reiterated below.

The written description sets forth a catalog of various generic types of agents that may possibly meet the requirements of the claims. For example, the specification teaches that the agent may be an "apoE inhibitor" (page 10, line 2). Furthermore, the specification teaches that "the apoE inhibitor may be a number of different types of agents, such as small molecules, antibodies or binding fragments thereof, and the like" (page 10, lines 5-6). The specification also teaches that "agents are also found among biomolecules, including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof" (page 10, lines 15-17). Then, on page 14, the specification teaches that antisense nucleic acid molecules

are contemplated for use as agents in practicing the claimed invention (line 11). Finally, on page 16, lines 8-9, the specification teaches that catalytic nucleic acids molecules, such as ribozymes, could be used as agents.

However, the specification does not distinctly and specifically point out the identity of even one agent suitable for use in practicing the invention as claimed. The disclosure of a catalog of potentially effective agents is deemed an insufficient written description of the agent of the claims because it would not reasonably convey to the skilled artisan that Appellants had possession of the claimed invention at the time the application was filed.

(B) Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Ditschuneit *et al.*, as evidenced by the disclosures of Pedreno *et al.* and Durrington *et al.* This ground of rejection of the claims under 35 USC § 102(b) is set forth in section 12 of the prior final Office Action, which was mailed January 13, 2003 (Paper No. 21), and has been briefly reiterated below.

Ditschuneit *et al.* teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides, namely type IIb hyperlipoproteinaemia, i.e., type IIb hyperlipidemia. More specifically, Ditshuneit *et al.* teaches a method comprising administering to the patients an effective amount of gemfibrozil to reduce the concentrations of both VLDL and triglycerides in the patient's serum.

Pedreno *et al.* teaches that treatment of patients having familial hypertriglyceridemia, or type IV hyperlipidemia, by gemfibrozil therapy results in a significant decrease in the levels of triglyceride, VLDL, and apoE in the plasma of the patients. Moreover, Pedreno *et al.* teaches that gemfibrozil therapy results in a decrease in the apoE content of VLDL in the plasma of the patient. Durrington *et al.* teaches that a method for treating a patient having type IIb hyperlipoproteinaemia, or type IIb hyperlipidemia, comprising administering to the patient an effective amount of gemfibrozil to cause a reduction in the concentrations of triglyceride and very low density lipoprotein (VLDL) in a patient's serum.

(C) Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Yoshino *et al.* This ground of rejection of the claims under 35 USC § 102(b) is set forth in section 13 of the prior final Office Action, which was mailed January 13, 2003 (Paper No. 21), and has been briefly reiterated below.

Yoshino *et al.* discloses a method for treating a patient having hyperlipoproteinaemia type IIb, i.e., type IIb hyperlipidemia, which comprises administering to the patient an effective amount of pravastatin to reduce the level of apoE in the serum of the patient. Yoshino *et al.* discloses that pravastatin therapy in patients having type IIb hyperlipidemia associated with non-insulin dependent diabetes results in a significant decrease in the levels of triglyceride, VLDL, and apoE in the plasma of the patients.

(D) Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Connor *et al.* This ground of rejection of the claims under 35 USC § 102(b) is set forth in section 14 of the prior final Office Action, which was mailed January 13, 2003 (Paper No. 21), and has been briefly reiterated below.

Connor *et al.* teaches a method for treating type IIb combined hyperlipidemia and type IV hyperlipidemia comprising administering dietary n-3 fatty acids. Connor *et al.* teaches that the treatment results in a dramatic reduction in plasma triglycerides, as well as a decrease in the levels of VLDL and apoE.

(E) Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Kasiske *et al.*, as evidenced by the disclosures of Wyne *et al.* This ground of rejection of the claims under 35 USC § 102(b) is set forth in section 15 of the prior final Office Action, which was mailed January 13, 2003 (Paper No. 21), and has been briefly reiterated below.

Kasiskie *et al.* teaches a method for treating patients diagnosed with a hyperlipidemia. The method of Kasiskie *et al.* involves administering to a patient an effective amount of lovastatin, an inhibitor of hydroxymethylglutaryl (HMG)-CoA reductase, to reduce the production of VLDL in the patient to reduce the level of VLDL in the plasma of the patient.

As evidenced by the teachings of Wyne *et al.*, mevinolin, i.e., lovastatin, attenuates the production of mRNA encoding apoE in cells and accordingly acts by a mechanism that involves reducing the expression of apoE.

(11) Response to Argument

(A) ***35 U.S.C. § 112, first paragraph: Written Description***

At pages 11-15 of the Brief, Appellants have traversed the grounds of rejection of claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 112, first paragraph arguing that the description of the claimed invention set forth in the disclosure would be sufficient to reasonably convey to the skilled artisan that the inventors had possession of the claimed invention at the time the application was filed.

At page 13 of the Brief, Appellants have argued, "the specification provides a description of at least three types of agents that can be used in the claimed methods" (Brief, page 13, paragraph 1; underlining in the original). Appellants have further stated that these at least three types of agents that are described in the specification are:

(a) Small Molecules;

(b) Antisense Molecules; and

(c) Ribozymes.

It is noted that Appellants have omitted antibodies, which have most certainly been contemplated for use as the agent to which the claims refer at page 10, paragraph 2 of the specification, for example. Nevertheless, the specification describes the members of these classes, or of the genus of agents as a whole, which are suitable for use in practicing the claimed invention, as commonly having the functional property of, when administered to a host, reducing the expression of apoE by an amount sufficient to

reduce the production of very low density lipoproteins (VLDL) in the host in order to reduce the plasma level of VLDL in the host.

At page 13, paragraph 3 of the Brief, with regard to antisense molecules, which the specification discloses could be used as the unspecified agent of the claims in practicing the claimed invention, Appellants have argued:

> Because the nucleotide sequences of apoE mRNAs are known, the sequences of antisense are also known, and need not be provided in the specification. [Appellants] note that it is well established that a "patent need not teach, and preferably omits, what is well known in the art." MPEP §2164.01.

Then, beginning at page 14, Appellants have argued that Charpentier *et al.* "**have already demonstrated that antisense technology can be used to reduce ApoE expression**" (Brief, page 15, paragraph 1; emboldened in the original).

Thus, it appears that Appellants have contended that the prior art teaches that the amount of plasma active apoE in a host can be reduced by administering to the host, an antisense molecule comprising the antisense nucleotide sequence of a messenger RNA (mRNA) molecule encoding apoE and it is therefore not necessary that the disclosure describe the antisense molecules, which can be so used, to have adequately described the claimed invention in a manner that might reasonably convey to the skilled artisan that the inventors had possession of the claimed invention at the time the application was filed. Yet, Charpentier *et al.* is not prior art. Moreover, as noted in the Office action mailed May 15, 2002 (Paper No. 18), supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification

lacks. See MPEP § 2164.05(a). In view of the preponderance of factual evidence of record, and contrary to Appellants' assertions, the claimed invention would not have been enabled by disclosures of the prior art at the time the application was filed, and certainly more guidance than that which is disclosed in the specification would have been necessary to reasonably convey to the skilled artisan that Appellants had possession of the claimed invention at that time.

Beginning at page 13 of the Brief, Appellants have argued, contrary to the factual evidence provided as part of the basis of the rejection, that the art of antisense chemistry and medicine is not unpredictable; and given the polynucleotide sequence of a messenger RNA (mRNA) molecule encoding any molecular target, the skilled artisan can reliably predict the structure of an antisense molecule that can be used to inhibit the expression of the molecular target. Furthermore, Appellants contend that the skilled artisan routinely designs and uses such an antisense molecules and can do so without need of performing an undue amount of complex experimentation. At page 14 of the Brief (paragraph 2), with regard to the teachings of Sohail *et al.*, for example, Appellants have argued:

> Thus, one cannot conclude from reading Sohail that antisense technology as a whole is unpredictable, since empirical determination of antisense sequences results in success. At most one can conclude that some experimentation is involved to identify an antisense nucleic acid that will hybridize with a given sense nucleic acid. As discusses above, a substantial amount of experimentation is allowed, if it is routine; and such experimentation would in fact be routine.

Thus, it appears that Appellants have contended that the type of experimentation necessary to identify a suitable antisense molecule, which might be used as the unspecified agent of the claims in practicing the claimed invention, would be substantial but routine. Therefore, Appellants have apparently argued that it would not be necessary to describe the particular and detailed structure of any one species of antisense molecule to have fulfilled the requirements set forth under 35 U.S.C. § 112, first paragraph, or to reasonably convey to the skilled artisan that Appellants had possession of the claimed invention at the time the application was filed by having merely described the potential of members of a genus of antisense molecules, which commonly comprise an antisense nucleotide sequence complementary to the sense nucleotide sequence of the gene encoding apoE, and a means for identifying which, if any can be used to practice the claimed invention.

Appellants' arguments have been carefully considered but have not been found persuasive for the following reasons.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Accordingly, so that one of ordinary skill in the art given benefit of the disclosure, would recognize that Appellants invented that which is claimed in the application, the disclosure must describe the subject matter encompassed by the claims in sufficient detail to reasonably convey to the skilled artisan that the Appellants had possession of that subject matter at the time the application was filed. Therefore, to meet the written description requirement, the disclosure must do more than merely describe a means for making and using the invention. To meet the written description requirement, the disclosure must include a description of at least a substantial, or at least a representative number of embodiments of the methods encompassed by the claims, and of sufficient detail to satisfy a factual inquiry to determine whether the skilled artisan would have reasonable cause given only benefit of Appellants' original disclosure, to accept the assertion set forth in the claims that Appellants had possession of the claimed invention as of the filing date sought.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual

reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). However, as noted in the previous Office actions, factual evidence of an actual reduction to practice has not been disclosed by Appellants in the specification; nor have Appellants shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor have Appellants described distinguishing identifying characteristics sufficient to show that Appellants were in possession of the claimed invention at the time the application was filed.

Moreover, the claims encompass a large genus of widely variant species and thus an adequate written description of the claimed invention must include sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Appellants were in possession of the claimed genus. The *Guidelines* (*Id.*) state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106). The preponderance of factual evidence of record establishes that at the time the application was filed, the art was in its infancy and was associated with a high degree of unpredictability, necessitating prior empirical determinations of which, if any agents might be used to practice the claimed methods with a reasonable expectation of success. Accordingly, it follows that an adequate

written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Again, however, it is appropriately noted that the disclosure is devoid of a showing of factual evidence of a reduction to practice of any one species of the claimed invention in which the structural and functional features of a member of the genus of agents to which the claims refer are particularly described in a manner such that the skilled artisan could instantly recognize, or envision the species.

Contrary to Appellants' contention, the art is not mature. As noted in the previous Office actions, the courts have determined that antisense technology is highly unpredictable. See *Enzo Biochem Inc. v. Calgene Inc.*, 52 USPQ2d 1129 (CAFC, 1999). Again, although the court acknowledged:

> In view of the rapid advances in science, we recognize that what may be unpredictable at one point in time may become predictable at a later time. See *Vaeck*, 947 F.2d at 496, 20 USPQ2d at 1445 (" [W]e do not imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than the particular species disclosed in their specification.").

(*Id.* at 1143), as evidenced by the teachings of Sohail *et al.*, Pierce *et al.*, and Lesson-Wood *et al.*, the time that antisense technology has advanced to the point of predictability has not yet arrived. The *Guidelines* state, "for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession" than would be required if the relevant art were mature (*Id.* at 1106).

Although the claims are not limited to methods in which said agent is an antisense oligonucleotide, the structures of at least a substantial number of oligonucleotides, or of at least a representative number of oligonucleotides that might be used to successfully practice the claimed invention have not been disclosed. In view of the teachings of Sohail *et al.* and Pierce *et al.*, the disclosure of a non-limiting example of a target of an antisense oligonucleotide does not constitute a sufficient description of the genus of oligonucleotides, or of the claimed genus of methods in which said agent is an oligonucleotide to reasonably convey to one skilled in the art that Appellants had possession of the claimed invention at the time the application was filed.

Furthermore, as noted in the previous Office action, despite the disclosure of a list of agents that might be used in practicing the claimed invention, the disclosure of such a "laundry list" of agents does not constitute a written description of every species in the claimed genus, as it would not reasonably lead those skilled in the art to any particular species. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Additionally, the courts have decided, "[i]t is not sufficient to define the recombinant molecule by its principal biological activity, e.g., having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property" (*Colbert v. Lofdahl*, 21 USPQ2d, 1068, 1071 (BPAI 1992)). Analogously, therefore, the recitation of a limitation requiring the agent to which the claims refer be capable of reducing the amount of plasma active apoE in said host by reducing the expression of apoE by an amount

sufficient to reduce VLDL production in said host does not constitute an adequate description of the claimed genus, or an adequate description of a representative number of species by disclosure of relevant, identifying characteristics to show the Appellants were in possession of the claimed genus at the time the application was filed.

The *Guidelines* (*Id.*) state that if the Examiner were unable to provide evidence and sound scientific reasoning to support the position that the written description requirement set forth under 35 USC § 112, first paragraph is not met, then there is a strong presumption that an adequate written description of the claimed invention is present in the application as originally filed. However, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption" (*Id.* at 1107). As sufficient evidence and sound scientific reasoning have been applied in support of the Office's position, the grounds of rejection under 35 USC § 112, first paragraph set forth in the previous Office Actions are entirely appropriate and proper.

Additionally, the *Guidelines* (*Id.*) state that rejection of an original claim for lack of written description should be rare. However, the *Guidelines* further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The prior art teaches several small molecule agents, and the prior art of record teaches at least four, which are markedly different in structure, yet, each of which, namely gemfibrozil, prevastatin, dietary n-3 fatty acids, and mevinolin

(lovastatin) have been used to treat a disease condition associated with an elevated plasma level of very low density lipoproteins (VLDL) and/or to reduce the plasma level of VLDL in a host by a mechanism that involves reducing the level of apoE that is expressed in the host. Again, the specification merely describes the members of the genus as commonly having the sought-after property of, when administered to a host, reducing the level of apoE expressed in the host, while failing to describe the detailed structure of any one species of the genus of unspecified agents to which the claims refer. It is therefore duly noted that that as disparate are the chemical structures of the agents disclosed by the prior art of record, which are capable of reducing the expression of apoE, the disclosures of the prior art, then, are deemed to constitute factual evidence that the skilled artisan would not have recognized that Appellants had possession of the claimed invention at the time the application was filed, because the specification fails to describe any *structural* feature that is commonly shared by the agents of the prior art, which might enable the skilled artisan to recognize and distinguish at least a reasonable number of the members of the genus of unspecified agents to which the claims refer from other small molecules that cannot be used to practice the claimed invention.

In summary, Appellants' disclosure does not include a description of at least a substantial number of embodiments of the methods encompassed by the claims; nor does Appellants' disclosure include a description of at least a representative number of embodiments of the methods encompassed by the claims. Accordingly, a skilled artisan in the relevant art would not reasonably conclude that Appellants had possession of the

claimed invention at the time the application was filed and therefore the disclosure is considered insufficient to meet the written description requirement of 35 USC § 112, first paragraph.

(B) ***35 U.S.C. § 102(b): Anticipation by the Prior Art***

At pages 24-33 of the Brief, Appellants have traversed the grounds of rejection of claims 1, 4-8, and 11 as being anticipated by Ditschuneit *et al.*, as evidenced by Pedreno *et al.* and Durrington *et al.*; claims 1, 4-8, and 11 as being anticipated by Yoshino *et al.*; claims 1, 4-8, and 11 as being anticipated by Connor *et al.*; and claims 1, 5, 6, and 11 as being anticipated by Kasiskie *et al.*, as evidenced by Wyne *et al.* In general, Appellants have argued that none of the cited prior art references discloses the claimed invention, because none of the references teaches the use of an agent, which when administered to a host, reduces the "transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE" (Brief, page 25, paragraph 3).

In reply to Appellants' general arguments, the claims do not recite a limitation requiring the agent be administered to the host in an amount effective to reduce "the transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE", rather the claims merely recite that the amount administered to the host be effective to reduce "the amount of plasma [or according to claim 5, the plasma amount of] active apoE in said host by reducing the expression of apoE by an amount sufficient to reduce VLDL production in said host". Accordingly, the mechanism by which agent effects the reduction in the expression of apoE is not limited by the claims; any agent, which when

administered to a host, causes a reduction in the amount of apoE that is "expressed", or which is present at the time of sampling in the host to whom the agent is administered would appear to fulfill the requirements of the claims, absent a showing of any difference. Appellants have argued that the skilled artisan would understand the phrase, namely "reducing the expression of apoE" to refer to "reducing the transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE" (Brief, page 25, paragraph 3), the Examiner disagrees; the interpretation of the phrase would be more broadly interpreted by the skilled artisan and would in part, be contextual in nature. For example, if the claims were limited to a method comprising administering to a host an antisense molecule, thereby "reducing the expression of apoE", the skilled artisan would then interpret the phrase "reducing the expression of apoE" as effectively reducing the level of translation of apoE, since, for example, Lesson-Wood *et al.* teach, "the mechanism of antisense ODN [i.e., oligodeoxynucleotide] action is thought to be via complementary hybridization with mRNA target sequences and subsequent degradation of DNA-RNA duplexes by RNaseH" (Lesson-Wood *et al.*, page 168, column 1, paragraph 2). However, as noted above, the claims are not limited to a method comprising administering to a host an agent that causes the direct inhibition of transcription of the gene encoding apoE; nor are the claims limited to an agent that causes the direct inhibition of translation of a mRNA molecule encoding apoE. If, for example, the claims were specifically drawn to a method comprising administering to a host an antibody, thereby "reducing the expression of apoE", the skilled artisan would then *not likely* interpret the phrase "reducing the expression of apoE" as directly and

effectively reducing the level of transcription of the gene encoding apoE, or directly and effectively reducing the level of translation of apoE, since transcription and translation are intracellular processes, and the skilled artisan would not expect the antibody to be taken up by the cell in order to interfere with those processes. Instead, if the recited agent were an antibody, the skilled artisan might expect that antibody to be capable of "reducing the expression of apoE" by a mechanism involving, perhaps, the inhibition of signal transduction via a receptor at the cell surface, thus blocking a signal that would otherwise stimulate the "expression of apoE".

The On-Line Medical Dictionary denotes "expression" as a term of "molecular biology" and defines it as follows: "The process by which a gene's coded information is converted into the structures present and operating in the cell" (The On-line Medical Dictionary, World-Wide Web URL: http://cancerweb.ncl.ac.uk/omd/index.html; published at the Dept. of Medical Oncology, University of Newcastle upon Tyne, © Copyright 1997-2003 - The CancerWEB Project, All Rights Reserved). The skilled artisan appreciates that the process by which a gene's coded information is converted into structures present and operating in the cell, or for that matter, outside the cell, if the structure is secreted, or exported, is highly complex and notably, involves more than just transcription and translation. Moreover, the skilled artisan appreciates that the process by which a gene's coded information is converted into structures present and operating in the cell, or for that matter, outside the cell, such as active plasma apoE, might involve transcription, mRNA processing and maturation, nuclear export,

translation, post-translational processing, modification, and maturation, intracellular trafficking, and secretion or export.

Again, other than a reduction in the level of transcription of the gene encoding apoE, or a reduction in the level of translation of a messenger RNA (mRNA) molecule encoding apoE, the skilled artisan would also certainly consider the claims to encompass a method comprising administering an agent that causes a reduction in the level of post-translational processing of the nascent apoE polypeptide, or still further, a reduction in the level of secretion of the mature apoE polypeptide, either of which are examples of mechanisms, which in addition to mechanisms involving reductions in transcription and translation, might reduce "the expression of apoE by an amount sufficient to reduce VLDL production in said host". Therefore, so long as the prior art discloses a method comprising administering to a host an amount of an agent that causes the amount of apoE in the host to be reduced, the limitations of the claims are deemed met by the disclosure of the prior art, particularly since Appellants have stated of record, "it necessarily follows that reducing the plasma level of active apoE will also reduce the plasma level of VLDL" (Paper No. 10, page 4, paragraph 2).

Then, beginning at page 26 of the Brief, Appellants have successively addressed the stated grounds of rejection of the claims under 35 U.S.C. § 102(b) as being anticipated by each of the prior art references, which were cited as the bases for the rejections.

(a) Regarding the rejection of the claims as being anticipated by Ditschuneit *et al.*, as evidenced by Pedreno *et al.* and Durrington *et al.*, Appellants have emphasized that their argument that the prior art is not anticipatory, since gemfibrozil does not reduce the expression of apoE. Appellants, however, have admitted that the prior art teaches a reduction in the level of plasma active apoE in the host to whom gemfibrozil is administered, but have contended, "**this decrease in apoE is not a decrease in expression of apoE**, as the claims require" (Brief, page 27, paragraph 1; emboldened in the original). Instead, Appellants have contended that the reduction in the plasma active apoE that occurs in the host treated with gemfibrozil results from the enhanced clearance of plasma VLDL particles from the host, of which apoE is a component. In reply to Appellants' arguments, it is duly noted that no factual evidence has been provided to support their contention that gemfibrozil reduces plasma active apoE in the host by enhancing the clearance of VLDL from the host, rather than actually causing "the expression of apoE" to be reduced. Such evidence, if it were provided, might show that despite unremitting levels of biosynthesis of apoE in the host treated with gemfibrozil, the levels of apoE in the host's plasma decrease following treatment, while increasing in the kidney or urine, for example. It is noted that Appellants have specifically referred to the disclosure at page 26388, right-hand column of Huang *et al.*, but no mention of gemfibrozil, or its mechanism of action, or its physiological effects in a host, are made. In the absence of evidence, Appellants' proposed mechanism of action of gemfibrozil, that is the physiologic means by which gemfibrozil reduces the level of apoE in the plasma of a host, is merely theoretical.

Furthermore, and contrary of Appellants' presumptive hypothesis, Pedreno *et al.* teach, "gemfibrozil affected the apoprotein composition of VLDL: total protein increased by 28%, the molar ratio of apoE to apoB decreased 64%, and apoE content decreased 55%" (abstract). If, as Appellants have hypothesized, gemfibrozil causes a reduction in the amount of plasma active apoE solely by enhancing the clearance of apoE-containing VLDL particles in the host treated with gemfibrozil, and without reducing the "expression of apoE" in the host, then why would the apoE content of VLDL particles in the host's plasma decrease, and the ratio of apoE to apoB also decrease? Contrary to "the common knowledge in the art" upon which Appellants' have purportedly based their presumptive hypothesis, if biosynthesis of apoE was unaffected by gemfibrozil, one would expect the apoE content of VLDL particles, if formed from newly synthesized components, in the host to remain constant. Moreover, because Durrington *et al.*, for example, teaches that gemfibrozil does not alter the concentration of apolipoprotein B, or apoB, one might not expect the ratio of apoE to apoB in VLDL particles to decrease in the VLDL of the host following treatment with gemfibrozil, unless the expression of apoE is adversely affected, or inhibited by gemfibrozil. On the other hand, if gemfibrozil does not reduce the expression of apoE, one would not expect the ratio of apoE to apoB to be affected by treatment with gemfibrozil.

Furthermore, Appellants have stated, "the common knowledge in the art [...] is that the mechanism of action of gemfibrozil is through increasing LDL expression" (Brief, in the paragraph bridging pages 26 and 27). Thus, Appellants have admitted that gemfibrozil is capable of directly affecting the "expression of" a gene or genes. If

gemfibrozil can affect the expression of one gene associated with the maintenance of particular concentrations of apolipoprotein in the plasma, why not another? As remarked in the Office action mailed May 15, 2002 (Paper No. 15), Clavey *et al.* teach that gemfibrozil is capable of directly affecting the expression of, i.e., the level of transcription of mRNA molecules encoding another apolipoprotein, namely apoCIII. Accordingly, it appears that gemfibrozil may generally affect transcription of genes involved in the homeostasis of apolipoproteins, perhaps by affecting the activity of a transcription factor that commonly regulates the expression of such genes. Clavey *et al.* suggests that the fibrates, or the class of drugs, including gemfibrozil, which are commonly used to treat hyperlipidemic and hypertriglyceridemic disorders, may affect the activity of one of the peroxisome-proliferator activated receptors (PPARs), which are transcription factors that regulate the expression of numerous genes that control metabolism. Unfortunately, Clavey *et al.* do not disclose the affect of gemfibrozil upon the transcription of the gene encoding apoE; nevertheless, it is noted that Clavey *et al.* teach that gemfibrozil affects the secretion of apoCIII, by affecting the transcription of the gene encoding apoCIII, and *similarly affects the secretion of apoE*, albeit to a less pronounced extent. As established in the previous Office actions, the mechanism or mechanisms by which gemfibrozil exerts its pharmacological effects is unknown or poorly understood; however, based upon the disclosure of Clavey *et al.*, it would not be unreasonable to expect that gemfibrozil affects the expression of the gene encoding apoE by reducing the transcription of the gene. Nonetheless, as evidenced by the

disclosure of Clavey *et al.*, it is overtly apparent that gemfibrozil acts to reduce "the expression of apoE", specifically by inhibiting its secretion.

In the absence of any factual evidence of record showing a difference, the method disclosed by the prior art and the claimed invention are deemed the same, since the prior art teaches that once administered to a host, gemfibrozil is capable of causing a reduction in the amount of plasma active apoE in the host, which concomitantly leads to a reduction in the amount of plasma VLDL in the host. As the Office does not have the facilities for examining and comparing the product of the prior art with the unspecified agent of the claims in order to establish that the product of the prior art does not possess the required material, structural, and functional characteristics of the unspecified agent, namely the ability to reduce the "expression of apoE by an amount sufficient to reduce VLDL production by at least two fold", the burden is upon Appellants to prove that agent of the prior art and the agent of the claims are different, so as to establish that the method disclosed by the prior art and the claimed invention are different. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Finally, *arguendo*, if Appellants' hypothesis were to prove correct, and the mechanism by which gemfibrozil reduces plasma active apoE involves an upregulation of LDL receptor expression and accordingly, an enhanced clearance of apoE-containing VLDL particles, rather than a reduction in the level of transcription or translation, would the effect *observed* not be a reduction in the "expression of apoE", as required by the

claims? The Examiner disagrees with Appellants' assertion that the skilled artisan would understand the phrase, namely "reducing the expression of apoE" to refer to "reducing the transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE" (Brief, page 25, paragraph 3). To the contrary, the skilled artisan might ascertain the level of plasma active apoE in the host and reasonably conclude that the "expression of apoE" is reduced in the host, if the value of the level of plasma active apoE in the host was lower than the value of some arbitrarily chosen reference level, because the skilled artisan appreciates that the process by which a gene is "expressed", or converted into structures present and operating in the cell, or for that matter, outside the cell, such as active plasma apoE, is highly complex and might involve transcription, mRNA processing and maturation, nuclear export, translation, post-translational processing, modification, and maturation, intracellular trafficking, or secretion. Furthermore, the skilled artisan appreciates that a pharmacological agent, such as gemfibrozil may act indirectly to reduce the "expression of apoE" by, for example, inhibiting signal transduction. Appellants have argued: "The Examiner has presented no evidence whatsoever that gemfibrozil affects the expression of apoE" (Brief, page 27, paragraph 3); but to the contrary, the prior art teaches that gemfibrozil is capable of reducing the "expression of apoE", absent a showing otherwise. For these reasons, also, the prior art is deemed anticipatory of the claimed invention, absent a showing of any difference between the recited agent and gemfibrozil, or any of the other agents disclosed by the prior art that appear to capable of reducing the expression, or level of plasma active apoE in a host.

(b) Regarding the rejection of the claims as being anticipated by Yoshino *et al.*, Appellants have argued at page 29, paragraph 2 that the prior art is not anticipatory for the following reasons:

> As discussed above for gemfibrozil, there is no evidence that pravastain acts to decrease VLDL production by reducing the expression of apoE, while there is evidence that it acts through a different mechanism in that it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

In reply to this argument, the fact that pravastatin is an inhibitor of HMG-CoA does not suggest that the inhibition of HMG-CoA does not affect the expression of the gene encoding apoE, or that pravastatin is not also an inhibitor of the expression of apoE. It remains entirely possible that pravastatin reduces the transcription of the gene encoding apoE, or the translation of the mRNA molecules encoding apoE by an indirect mechanism involving inhibition of HMG-CoA, or by some other mechanism through which the drug exerts its reducing effects upon the level of apoE in the plasma of a host treated with the drug. In this regard, as remarked in the Office action mailed May 15, 2002 (Paper No. 15), Wyne *et al.* disclose that another drug of the same class, i.e., a known inhibitor of HMG-CoA reductase, is capable of attenuating the stimulation of transcription of the gene encoding apoE in a dose-responsive manner. As established in the previous Office actions, the mechanism or mechanisms by which pravastatin exerts its pharmacological effects is unknown or poorly understood; regarding the effect of pravastatin upon LDL-cholesterol, for example, Yoshino *et al.* discloses, "the mechanism by which pravastatin suppresses plasma cholesterol levels in these two

conditions [namely, non-insulin dependent diabetes and non-diabetic hypercholesterolemia] may differ. However, based upon the disclosure of Wyne *et al.*, it would not be unreasonable to expect that the class of compounds, which includes pravastatin, to act at least in part by a mechanism that involves reducing the expression of the gene encoding apoE.

Again, Appellants have proposed a hypothesis to explain the ability of pravastatin to reduce the expression of apoE in a host, in which the inhibition of HMG-CoA by pravastatin leads to an upregulation of expression of LDL receptor; and as with gemfibrozil, the increased expression of LDL receptor causes the enhanced clearance of VLDL particles containing apoE. However, again, it is duly noted that Appellants have provided no factual evidence to support their contention that pravastatin reduces plasma active apoE in the host by enhancing the clearance of VLDL from the host, rather than actually causing "the expression of apoE" to be reduced. Such evidence, if it were provided, might show that despite unremitting levels of biosynthesis of apoE in the host treated with pravastatin, the levels of apoE in the host's plasma decrease following treatment, while increasing in the kidney or urine, for example.

At page 29, Appellants have argued, "if pravastatin decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE, but it does not" (Brief, page 29, paragraph 2). Still, the prior teaches that pravastatin decreases plasma active apoE, and concomitantly reduces VLDL, in the host.

On the basis of the disclosure of Huang *et al.*, Appellants have argued, "increased apoE results in normal or decreased LDL levels; however, Yoshino shows a significant decrease in LDL cholesterol levels after 6 months of treatment with pravastatin and a further decrease by the 12th month of treatment" (Brief, page 29, paragraph 2; underlining in the original). In reply, and to the contrary, if LDL is produced from VLDL by lipolytic processing, as Appellants have indicated, since the amount of VLDL decreases upon treatment with pravastatin, one *would* expect plasma LDL to decrease, just as the prior art teaches. Because VLDL decreases following treatment with pravastatin, the production of LDL by the lipolytic processing of VLDL is also expected to decrease.

In the absence of any factual evidence of record showing a difference, the method disclosed by the prior art and the claimed invention are deemed the same, since the prior art teaches that once administered to a host, pravastatin is capable of causing a reduction in the amount of plasma active apoE in the host, which concomitantly leads to a reduction in the amount of plasma VLDL in the host. As the Office does not have the facilities for examining and comparing the product of the prior art with the unspecified agent of the claims in order to establish that the product of the prior art does not possess the required material, structural, and functional characteristics of the unspecified agent, namely the ability to reduce the "expression of apoE by an amount sufficient to reduce VLDL production by at least two fold", the burden is upon Appellants to prove that agent of the prior art and the agent of the claims are different, so as to establish that the method disclosed by the prior art and the

claimed invention are different. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Finally, at page 30 of the Brief, Appellants have remarked, "Wyne does not discuss pravastatin" and "Wyne does not disclose that mevinolin, or any other inhibitor of HMG-CoA reductase, reduces apoE expression" (Brief, page 30, paragraph 2), apparently questioning the relevance of the disclosure of Wyne *et al.* to the disclosure of Yoshino *et al.* For added clarification, as noted above, Wyne et al. teaches that mevinolin, or lovastatin is an inhibitor of HMG-CoA reductase, as is pravastatin, and therefore a member of the same class of drugs as pravastatin. Wyne et al. teaches that mevinolin is capable of attenuating the stimulation of transcription of the gene encoding apoE in a dose-responsive manner. While Yoshino et al. does not explicitly teach that pravastatin is capable of directly inhibiting the *transcription* of the gene encoding apoE, as is mevinolin, Yoshino et al. discloses that lovastatin, or mevinolin is also an HMG-CoA reductase. The skilled artisan appreciates that drugs are generally classified according to similar structure and bioactivity; as lovastatin and pravastatin are related in structure and are both inhibitors of HMG-CoA reductase, and since lovastatin is capable of attenuating the stimulation of transcription of the gene encoding apoE in a dose-responsive manner, it is not unreasonable to expect that pravastatin is also capable of doing so.

(c) Regarding the rejection of the claims as being anticipated by Connor *et al.*, Appellants have argued at page 31, paragraph 3 that the prior art is not anticipatory for the following reasons:

> Nothing in Connor teaches that apoE is a target for reducing the levels of VLDL production or that reduction of apoE gene expression will cause a reduction in VLDL production. Furthermore, there is nothing that suggests that n-3 fatty acids act to decrease VLDL production by reducing apoE expression, while there is evidence that n-3 fatty acids act through a different mechanism.

As to these other mechanisms, Appellants have again proposed a hypothesis to explain the ability of n-3 fatty acids to reduce the expression of apoE in a host, which involves the enhanced clearance of apoE-containing VLDL from the host by the upregulated expression of LDL receptors upon treatment with dietary n-3 fatty acids. Again, Appellants refer the disclosure of Huang *et al.* and contend that the data presented therein supports their contention that since Connor *et al.* discloses that dietary n-3 fatty acids cause a reduction in LDL, the opposite effect upon LDL would be expected if n-3 fatty acids act by decreasing the expression of active apoE. As with the mechanism of action of pravastatin, Appellants have argued, "if the cited agent [here, dietary n-3 fatty acids] decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE" (Brief, page 31, paragraph 3; underlining in the original). However, in this instance, it is duly noted that Appellants have provided no factual evidence to support their apparent contention that n-3 fatty acids increase the level of LDL receptor expression, as might gemfibrozil and pravastatin; and additionally, Appellants have provided no factual

evidence to support the contention that dietary n-3 fatty acids reduce plasma active apoE in the host by enhancing the clearance of VLDL from the host, rather than actually causing "the expression of apoE" to be reduced. Such evidence, if it were provided, might show that despite unremitting levels of biosynthesis of apoE in the host treated with dietary n-3 fatty acids, the levels of apoE in the host's plasma decrease following treatment, while increasing in the kidney or urine, for example.

Again, to the contrary of Appellants' remarks, if LDL is produced from VLDL by lipolytic processing, as Appellants have indicated in reciting their hypothesis, since the amount of VLDL decreases upon treatment with dietary n-3 fatty acids, one *would* expect plasma LDL to decrease, just as the prior art teaches. Because VLDL decreases following treatment with dietary n-3 fatty acids, the production of LDL by the lipolytic processing of VLDL is also expected to decrease.

The prior teaches that treatments with dietary n-3 fatty acids decrease plasma active apoE, and concomitantly reduce VLDL, in the host. In the absence of any factual evidence of record showing a difference, the method disclosed by the prior art and the claimed invention are deemed the same, since the prior art teaches that once administered to a host, dietary n-3 fatty acids are capable of causing a reduction in the amount of plasma active apoE in the host, which concomitantly leads to a reduction in the amount of plasma VLDL in the host. As the Office does not have the facilities for examining and comparing the product of the prior art with the unspecified agent of the claims in order to establish that the product of the prior art does not possess the required material, structural, and functional characteristics of the unspecified agent,

namely the ability to reduce the "expression of apoE by an amount sufficient to reduce VLDL production by at least two fold", the burden is upon Appellants to prove that agent of the prior art and the agent of the claims are different, so as to establish that the method disclosed by the prior art and the claimed invention are different. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

At pages 31-32, Appellants have referred to the disclosures of Harris, Hebbachi *et al.*, and Anil *et al.*, arguing that these disclosures support their assertion that dietary n-3 fatty acids reduce synthesis of triglyceride and VLDL in the liver and shorten turnover of VLDL in the plasma to reduce the plasma level of VLDL, rather than by reducing VLDL production by reducing the expression of apoE, as the claims require. Appellants have remarked in particular that Anil et al. discloses that "the effect of n-3 fatty acids on hepatic VLDL production is mediated through prostaglandins" (Brief, page 32, paragraph 1) and therefore have argued: "Nothing in the references teach that dietary n-3 fatty acids reduce the expression of apoE or that reducing apoE expression will reduce VLDL production and consequently reduce the plasma VLDL level" (Brief, page 32, paragraph 1).

In reply, Harris teaches, "the mechanisms leading to the increases in LDL and HDL have not been determined" (Harris, abstract). However, Harris discloses: "When fish oil is fed and saturated fat intake is constant, LDL-C [LDL-cholesterol] levels either do not change or may increase" (Harris, abstract). Appellants have argued that the reduced LDL levels in host's treated with dietary n-3 fatty acids, as disclosed by Connor

et al., "is the opposite effect on LDL level that would be expected if n-3 fatty acids acted by decreasing active apoE by decreasing gene expression" (Brief, page 31, paragraph 3). Instead, Appellants have argued that if dietary n-3 fatty acids decrease VLDL production by reducing the expression of the gene encoding apoE, as the claims would require, LDL levels should increase, or possibly remain unchanged (as it is unclear what LDL levels Appellants might argue would result from the "opposite effect" of a treatment resulting in normal LDL levels). Indeed, Harris discloses that if dietary n-3 fatty acids are administered to the host, and saturated fat intake remains constant, LDL-cholesterol levels do, in fact, increase, or remain unchanged. Thus, contrary to Appellants' assertions, it appears the disclosure of Harris is not inconsistent with the findings of Connor *et al.*

Anil *et al.*, as Appellants have remarked, discloses, "the n-3 fatty acids may exert their effect on VLDL production by liver cells through prostaglandins" (Anil *et al.*, abstract). Prostaglandins are well known ligands of a family of transcription factors designated the peroxisome-proliferator activated receptors, or the PPARs, which are transcription factors that regulate the expression of numerous genes that control metabolism. As noted earlier, Clavey *et al.* suggests that the fibrates, or the class of drugs, including gemfibrozil, which are commonly used to treat hyperlipidemic and hypertriglyceridemic disorders, may affect the activity of one or members of the family of PPARs. Thus, the fact that Anil *et al.* discloses that the n-3 fatty acids may mediate the reduction in VLDL production through prostaglandins is not inconsistent with a premise that n-3 fatty acids reduce VLDL production by reducing the expression of apoE. The

disclosure of Anil et al., therefore, does not suggest that dietary n-3 fatty acids do not reduce VLDL production by reducing the expression of apoE; rather, the disclosure of Anil *et al.* might reasonably suggest that the fibrates, e.g., gemfibrozil, and the dietary n-3 fatty acids commonly decrease VLDL production by reducing the transcription of the gene encoding apoE.

Appellants' remarks regarding the disclosure of Hebbachi *et al.* are acknowledged; however, Hebbachi *et al.* disclose the effects of n-3 fatty acids upon the levels of expression of VLDL-associated triacylglycerol and apolipoprotein B, or apoB. Hebbachi et al. do not address the effects of n-3 fatty acids upon the level of expression of apoE. Nevertheless, the fact that upon treatment with n-3 fatty acids, hepatocytes secrete relatively lower amounts of VLDL-associated triacylglycerol and apoB, does not support the notion that n-3 fatty acids might not also reduce the level of expression of apoE by a similar mechanism.

(d) Regarding the rejection of the claims as being anticipated by Kasiske *et al.*, Appellants have argued at page 32, paragraph 5 that the prior art is not anticipatory for the following reasons:

> There is no evidence that in Kasiskie that lovastatin acts to decrease plasma VLDL levels by reducing expression of apoE. [...] Wyne states that HMG-CoA reductase is a rate-limiting enzyme in cholesterol synthesis and as such reduces the level of downstream products. Wyne does not disclose that mevinolin reduces apoE expression.

Appellants' arguments have been carefully considered but not found persuasive. Lovastatin, or mevinolin, as Wyne et al. discloses, attenuates the transcription of the

gene encoding apoE. This fact is irrefutably established by the disclosure of Wyne et al., particularly by the data presented in Figure 5. Therefore, Kasiske et al. teach a method comprising administering to a host, an effective amount of agent, namely lovastatin to reduce the expression of plasma active apoE by reducing the expression, specifically the transcription of the gene encoding apoE by an amount sufficient to reduce VLDL production and thereby reduce the plasma level of VLDL in the host, so treated.

Kasiske et al. do not explicity disclose the amount of lovastatin that must be administered to the host to reduce the plasma level of the host by at least two-fold. Nevertheless, lovastatin is deemed the same as the unspecified agent to which the claims refer, absent a showing of any difference.

Therefore, in the absence of any factual evidence of record showing a difference, the method disclosed by the prior art and the claimed invention are deemed the same, since the prior art teaches that once administered to a host, lovastatin is capable of causing a reduction in the amount of plasma active apoE in the host, which concomitantly leads to a reduction in the amount of plasma VLDL in the host. As the Office does not have the facilities for examining and comparing the product of the prior art with the unspecified agent of the claims in order to establish that the product of the prior art does not possess the required material, structural, and functional characteristics of the unspecified agent, namely the ability to reduce the "expression of apoE by an amount sufficient to reduce VLDL production by at least two fold", the burden is upon Appellants to prove that agent of the prior art and the agent of the claims

are different, so as to establish that the method disclosed by the prior art and the claimed invention are different. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Finally, as a more general comment, it is noted that, upon the basis of the disclosure of Huang et al., Appellants have repeatedly argued that the observed effects of gemfibrozil, pravastatin, and dietary n-3 fatty acids, which are disclosed by the prior art of record, are not those that would be expected, if these agents act by effectively reducing the expression of apoE. Appellants have argued if apoE expression were to decrease as a result of the treatments, LDL levels would not be expected to decrease, as has been observed, but should increase; this assertion is based upon the disclosure of Huang et al. showing that the over-expression of apoE in mice leads to the maintenance of normal levels, or increased levels of LDL. If Appellants' presumptions are correct, because lovastatin reduces LDL-cholesterol levels, lovastatin must not reduce the expression of apoE – but to the contrary, Wyne *et al.* discloses that it does!

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
August 4, 2003

Conferees:

Anthony Caputa, Ph.D.
Supervisory Patent Examiner
Art Unit 1642

Yvonne Eyler, Ph.D.
Supervisory Patent Examiner
Art Unit 1646

BRET FIELD
BOZICEVIC FIELD & FRANCIS LLP
200 MIDDLEFIELD ROAD
SUITE 200
MENLO PARK, CA 94025

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

J Rawlings

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
July 15, 2003

Conferees:

Anthony Caputa, Ph.D.
Supervisory Patent Examiner
Art Unit 1642

Yvonne Eyler, Ph.D.
Supervisory Patent Examiner
Art Unit 1646

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Confer

BRET FIELD
BOZICEVIC FIELD & FRANCIS LLP
200 MIDDLEFIELD ROAD
SUITE 200
MENLO PARK, CA 94025

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600